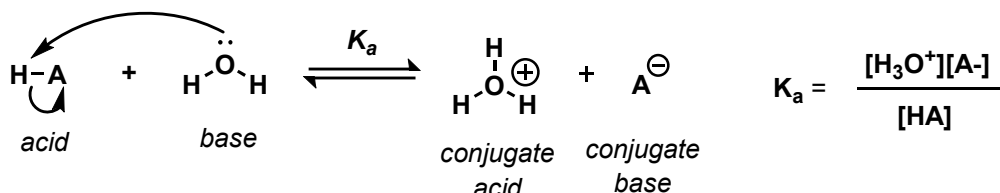


Chemistry 17: Section Handout 5

Topics: pK_a , acid-base equilibria, factors influencing acid strength, protonation states, pH, acyl transfer reactions

Key Concept Review

Acid-Base Equilibria: The Brønsted–Lowry theory of acidity defines acids as species that donate protons in a reaction. Bases are species that accept protons. To quantify the acidity of a compound, it is useful to consider the equilibrium constant, K_a , of the dissociation of that compound in water, assuming an infinitely dilute aqueous solution:



Traditionally, we use the negative logarithm of K_a , which is called pK_a (just as pH is the negative logarithm of $[\text{H}^+]$):

$$pK_a = -\log[K_a]$$

The smaller the pK_a of an acid is, the more acidic it is, and the more likely it is to give up its proton. The larger the pK_a of an acid, the less acidic it is, and the less likely it is to give up its proton. Most molecules you will encounter in organic chemistry have a pK_a between -10 and 50.

Factors Influencing Acid Strength: The acidity of a molecule depends on its thermodynamic stability relative to its conjugate base. Typically this will involve evaluating the relative stabilities of the charged components in the equilibrium. Note that we are focusing on thermodynamics here, as proton transfers are fast kinetically.

1. Element Effects: *Element effects include electronegativity and polarizability.*

More electronegative elements are better able to accommodate negative charge, thereby rendering protons attached to these atoms more acidic. Across a period, trend in increasing acidity follows the periodic electronegativity trend.

	H-CH ₃	H-NH ₂	H-OH	H-F
EN:	2.5 (C)	3.0 (N)	3.5 (O)	4.0 (F)
pK_a :	50	38	15.7	3

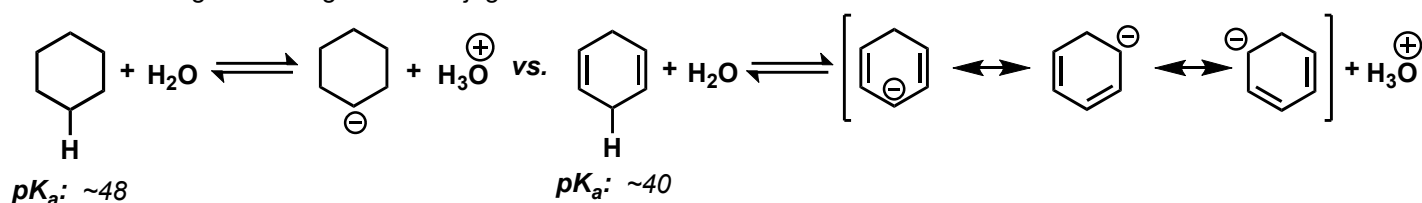
Larger elements (those lower in the periodic table) are **polarizable** due to their diffuse orbitals. These diffuse orbitals are able to spread negative charge over a large volume, analogously to delocalization, which is stabilizing. As a result, protons attached to larger, more polarizable atoms are more acidic. Down a group, the trend in increasing acidity follows the periodic trend in size.

	H-OMe	H-SMe	H-SeMe
pK_a :	15.5	10.4	5.2

2. Hybridization Effects: Orbitals with more s character lie closer to the nucleus, increasing their effective electronegativity and ability to stabilize negative charge. As such, protons attached at orbitals with more s character (for a given element) will be more acidic.

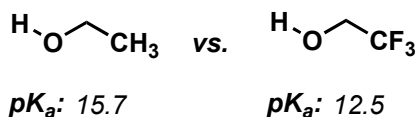
Hybridization:	sp^3	sp^2	sp
% s character	25	33	50
pK_a :	~50	44	25

3. Delocalization Effects: If the negative charge resulting from deprotonation can be delocalized, the conjugate base will be stabilized. As such, the molecule will be more acidic than an analogous molecule that cannot delocalize negative charge in its conjugate base.



This effect is even more significant for compounds where aromaticity is established upon deprotonation.

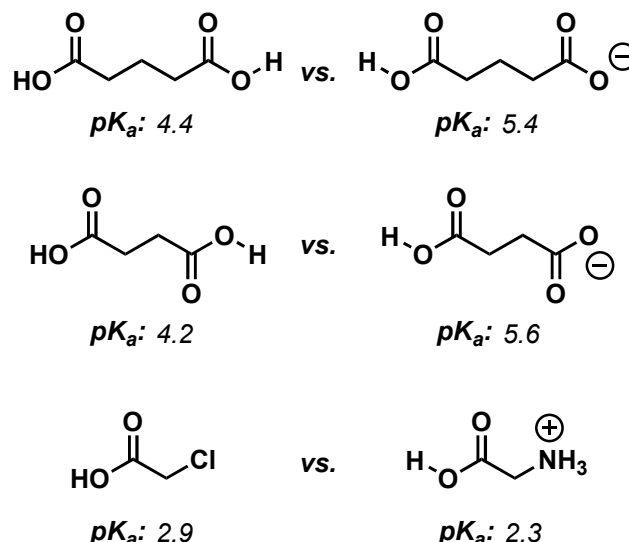
4. Inductive Effects: Electronegative substituents near acidic protons can increase acidity by inductively withdrawing electron density, thereby stabilizing the negative charge on the conjugate base.



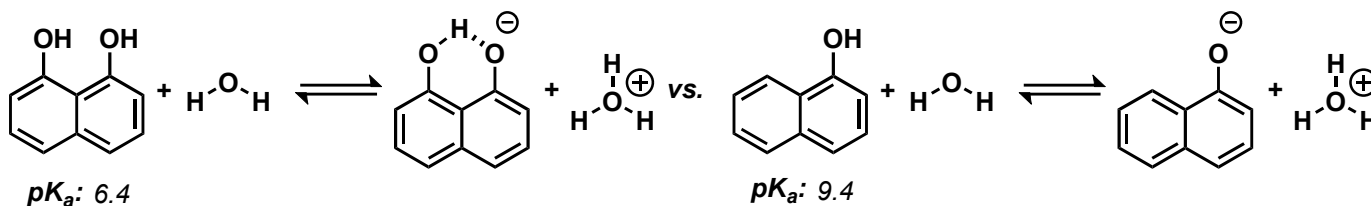
5. Charge/Electrostatic Effects: The presence of a charge in a molecule can have a significant effect on acidity, especially if the site of the charge is near the acidic proton.

A negative charge will destabilize another negative charge. That is why the first proton in the dicarboxylic acids shown is more acidic than the second proton. Also notice that the closer the two carboxylates are to one another, the greater the pK_a difference between them.

Conversely, a positive charge will stabilize a nearby negative charge; this contributes to the increased acidity of amino acids relative to isolated carboxylic acids (the inductive effect also plays a role).

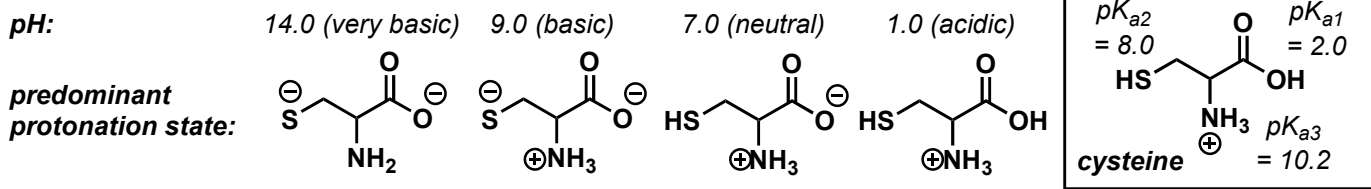


Intramolecular stabilizing interactions can similarly increase acidity. For example, deprotonation of the following diol forms a hydrogen bond-stabilized anion.

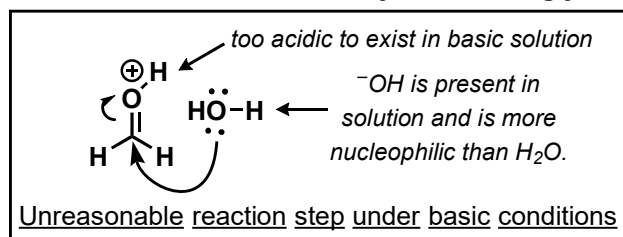
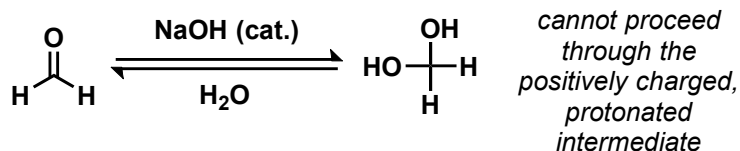


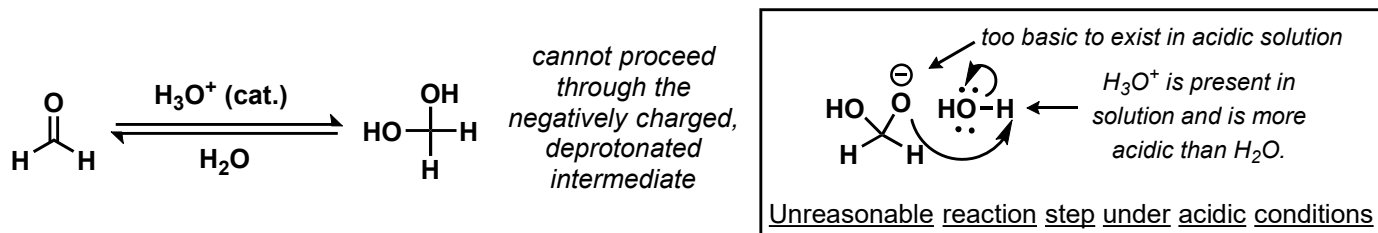
6. Medium Effects: Ionization is much more favorable in solvent than in the gas phase, because solvents can create a more polar environment (non-specific interactions) and form hydrogen bonds with the ions (specific interactions). Water is uniquely good at stabilizing ions due to its high polarity and its ability to act as both a hydrogen-bond donor AND a hydrogen-bond acceptor.

Protonation States as a Function of pH: To determine the predominant protonation state of a molecule at a given pH, use the pK_a of the individual acid/base sites. If the pH is lower than the pK_a , the site will be protonated. If the pH is higher than the pK_a , the site will be deprotonated.

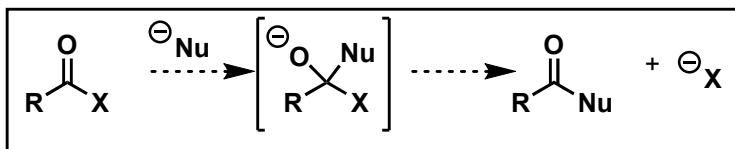


A reasonable mechanism cannot proceed through an intermediate in a protonation state incompatible with the reaction pH (cannot have base catalysis in strong acidic media, cannot have acid catalysis in strongly basic media).





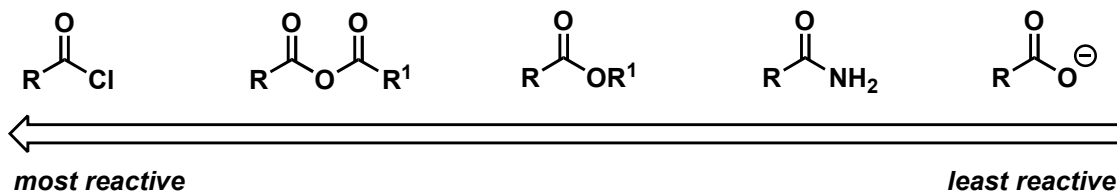
Acyl Transfer Reactions: If a carbonyl compound bears a leaving group (X), the tetrahedral adduct resulting from addition of a nucleophile to the carbonyl can collapse by ejecting X^- resulting in a new carbonyl derivative where the nucleophile has effectively replaced X. The RCO fragment is called an “acyl” group, so these reactions are called acyl transfer reactions.



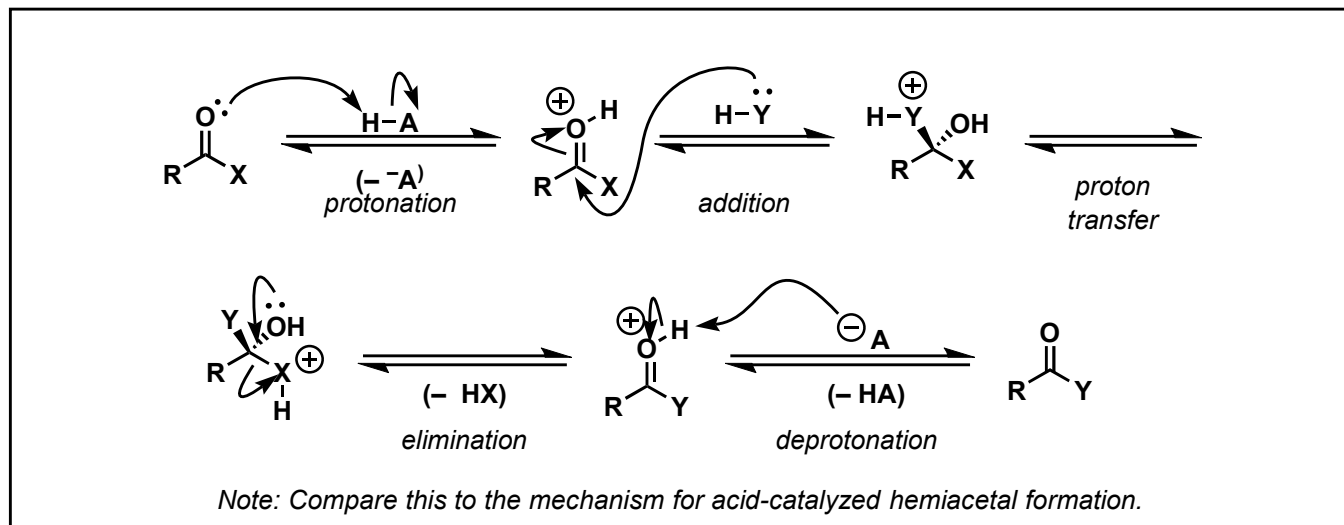
Acyl transfer reactions may proceed under acidic, strongly basic, and/or mildly basic conditions, depending on the following considerations.

- (1) Is the carbonyl group electrophilic enough to be attacked? (i.e. How low is its LUMO?)
- (2) Is the attacking group (Y^-) nucleophilic enough? (i.e. How high is its HOMO?)
- (3) Which is a better leaving group, X^- or Y^- ?
- (4) Is the product more or less reactive than the starting material?

Reactivity of Carboxylic Acid Derivatives: The carboxylic acid derivatives below are ordered according to their reactivity.



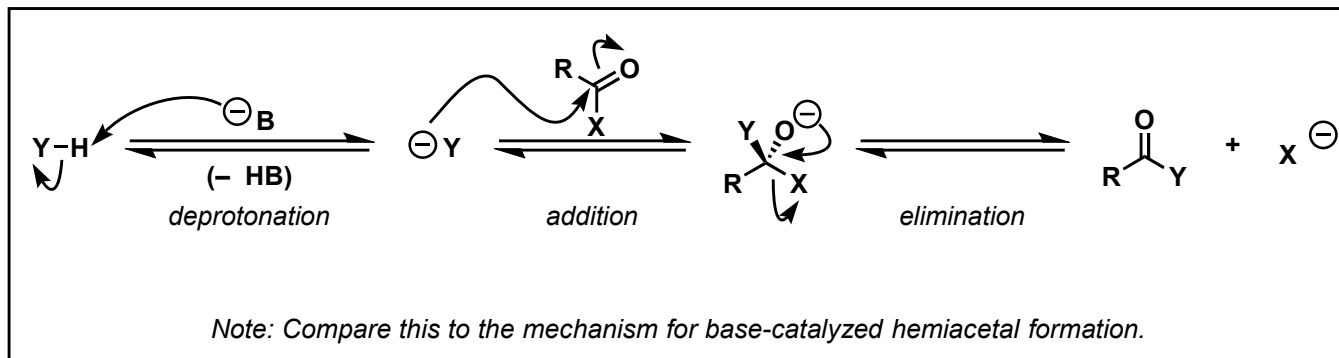
Acidic Conditions: Use acidic conditions to protonate the carbonyl. The resulting positive charge lowers the LUMO, making the electrophile more electrophilic.



Acyl transfer reactions can be performed under acidic conditions to achieve the following transformations:

- (1) esters to carboxylic acids (drive the reaction to completion by using excess water or by removing the alcohol coproduct)
- (2) carboxylic acids to esters (Fischer esterification; drive the reaction to completion by removing water)
- (3) amides to carboxylic acids

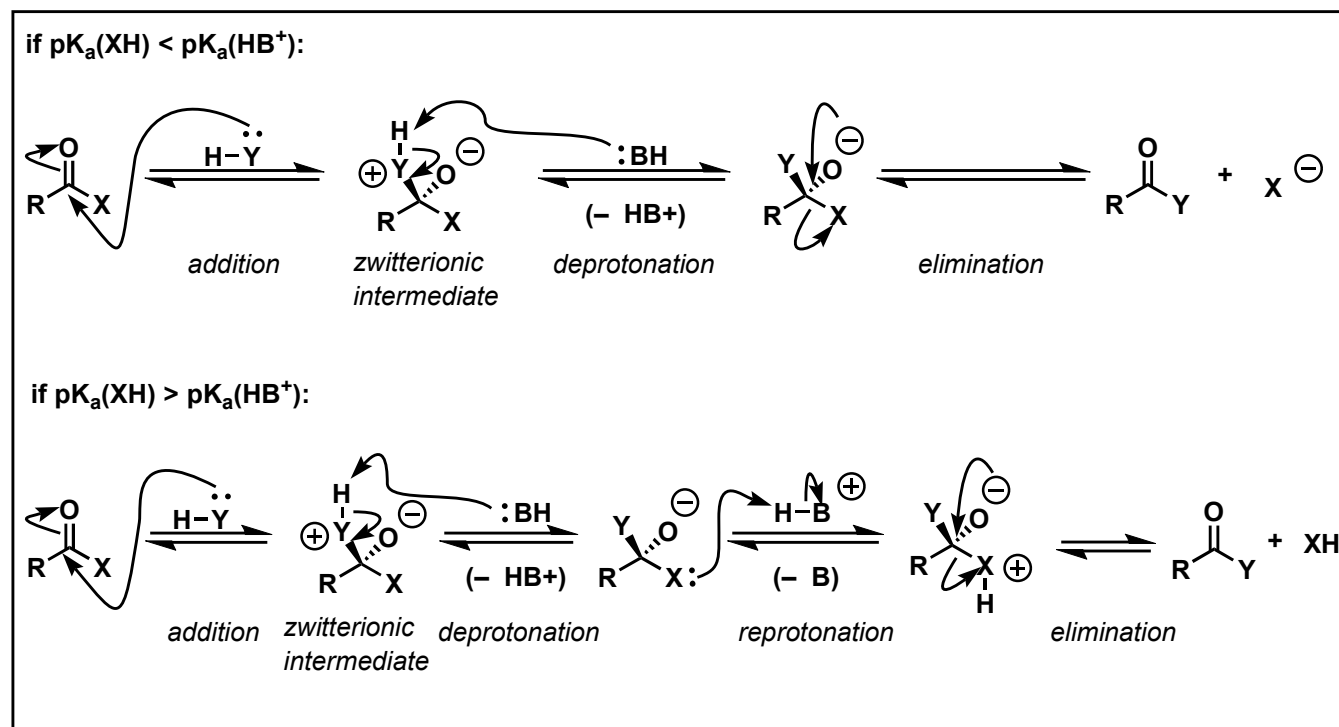
Strongly Basic Conditions: Use strongly basic conditions to deprotonate the nucleophile. The resulting negative charge raises the HOMO, making the nucleophile more nucleophilic. Strongly basic conditions require bases with $pK_{aH} \geq 12$; these are bases like hydroxide, alkoxides, Grignard reagents, alkyl lithium reagents, NaH, or $NaNH_2$.



Acyl transfer reactions can be performed under strongly basic conditions to achieve the following transformations:

- (1) esters to carboxylates (saponification; the reaction goes to completion because the alkoxide X^- then deprotonates the product carboxylic acid)
- (2) amides to carboxylates
- (3) acid chlorides or anhydrides to carboxylates
- (4) acid chlorides or anhydrides to esters or amides (possible, but not typically used)

Mildly Basic Conditions: Mild bases are not strong enough to deprotonate the neutral starting material but are strong enough to deprotonate the zwitterionic intermediate. Mildly basic conditions require bases with pK_{aH} in the range of 5–12; these are typically amines. Often an excess of an amine nucleophile will be added, so that it can also act as the base.



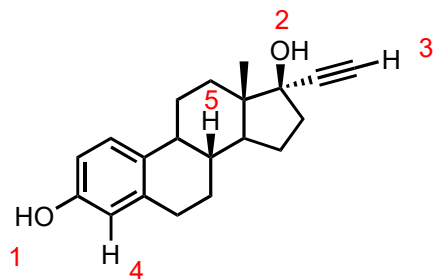
Acyl transfer reactions can be performed under mildly basic conditions to achieve the following transformations:

- (1) acyl chlorides to anhydrides, esters, amides, or carboxylic acids
- (2) anhydrides to esters, amides, or carboxylates
- (3) esters to amides

Workshop Problems

Workshop Problem 1: Acidity

1-a. Rank the 5 explicitly-drawn H's in the molecule below in order of acidity where 1 = most acidic. (Ethinyl estradiol is a molecule found in birth control pills.) Between each pair of ordered H's, indicate which one of the effects in the box below is *most* responsible for the difference in acidity. If resonance is invoked, draw the resonance of the conjugate base.



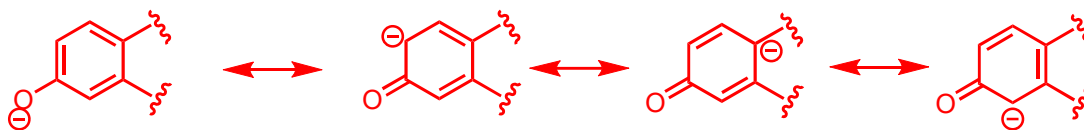
Ethinyl estradiol

1 vs 2 resonance / hybridization

2 vs 3 electronegativity (O vs C)

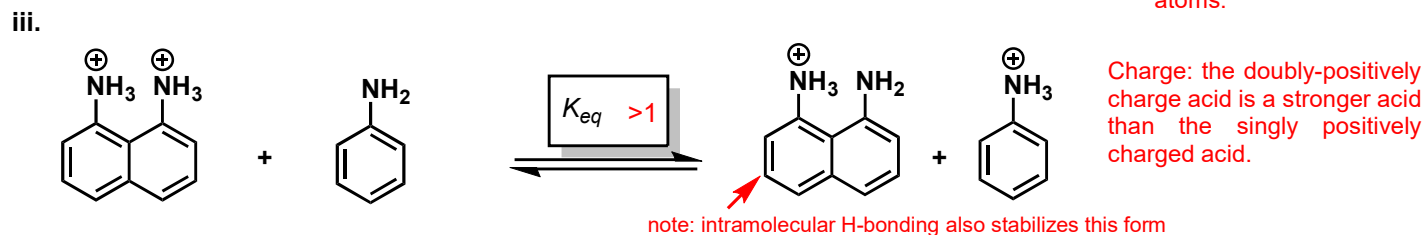
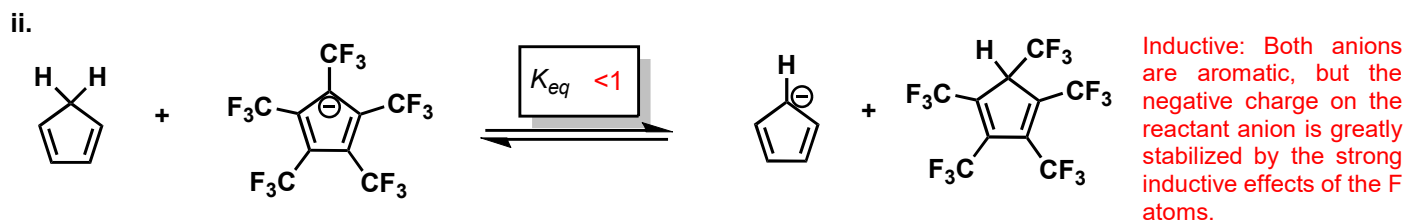
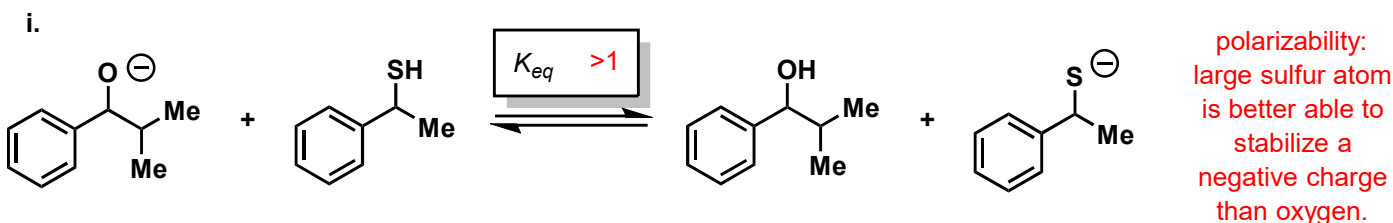
3 vs 4 hybridization (sp vs sp²)

4 vs 5 hybridization (sp² vs sp³)



These resonance structures are minor as the negative charge is on C, but delocalization of the lone pair requires it to be in a p-orbital and therefore the O is sp²-hybridized. Due to greater s-character, this orbital is better able to stabilize the negative charge than the sp³ orbital in the conjugate base of the alcohol.

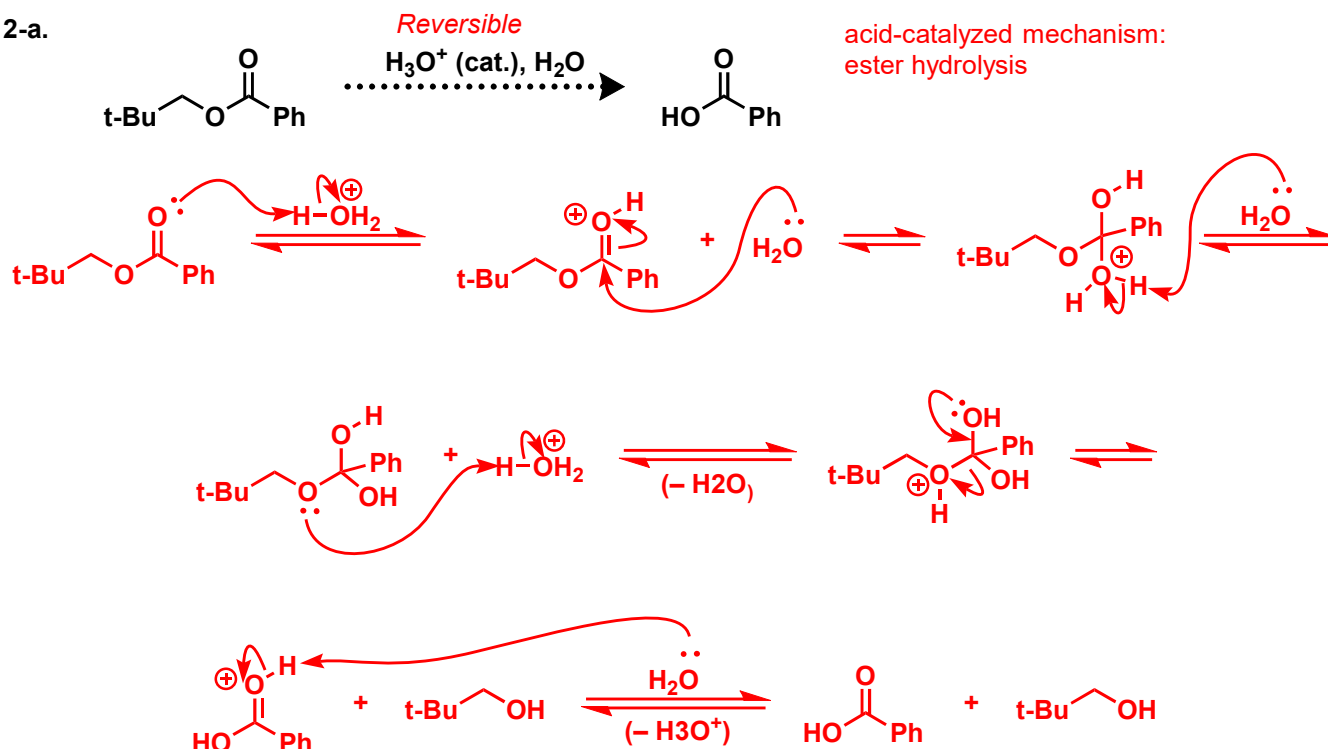
1-b. Consider each of the equilibria below; for each, indicate whether the K_{eq} is greater than, equal to, or less than 1. Briefly justify your choice.



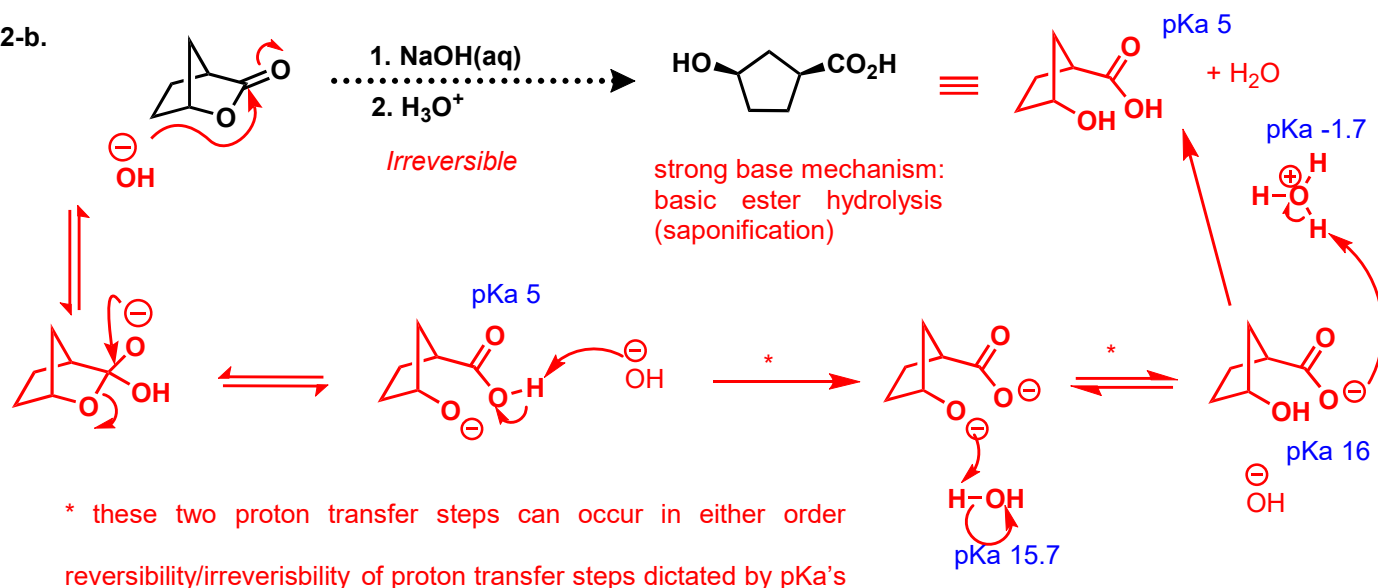
Workshop Problem 2: Acyl Transfer Reactions

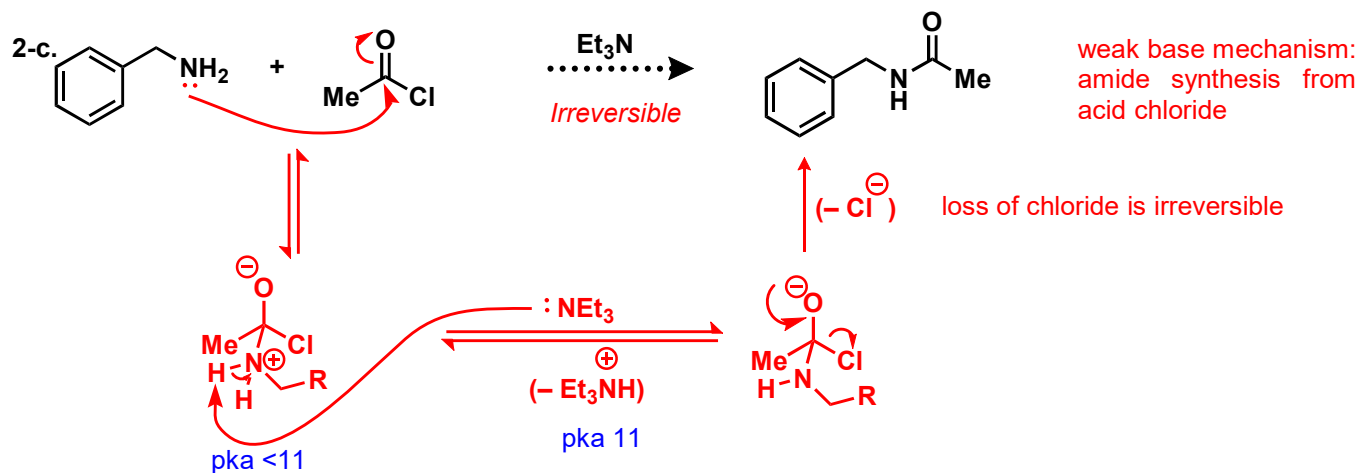
Propose a curved-arrow mechanism for each transformation below. Keep in mind the reactivity of the nucleophile, electrophile, and leaving group under the conditions provided, and make note of the reversibility or irreversibility of each step.

2-a.



2-b.



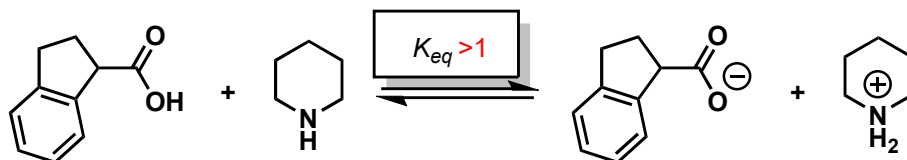


Practice Problems

Skillbuilder Problem 1: Acid-Base Equilibria

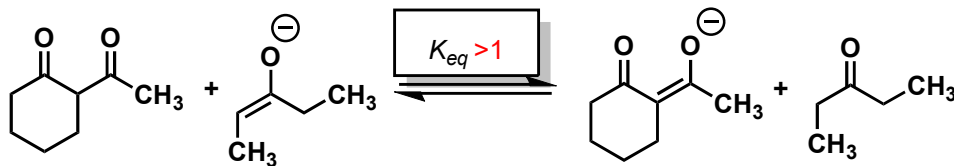
Consider each of the equilibria below; for each, indicate whether the K_{eq} is greater than, equal to, or less than 1. Briefly justify your choice.

1-a.



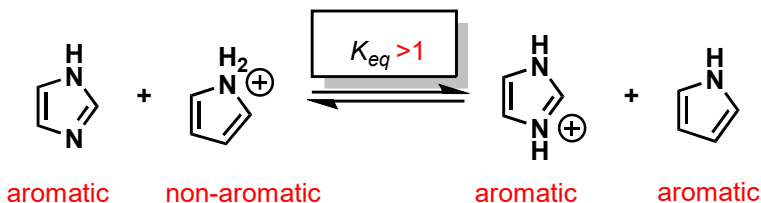
Carboxylate anions are highly stabilized by delocalization between two oxygen atoms.

1-b.



The conjugate base of the 1,3-diketone is more extensively stabilized through access to more resonance structures/greater delocalization than the conjugate base of the isolated ketone.

1-c.



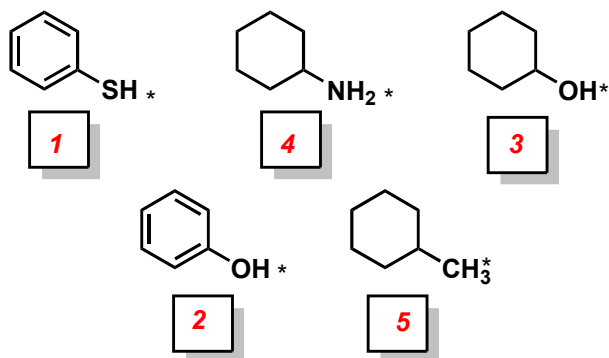
Protonation of pyrrole breaks aromaticity, but protonation of imidazole does not.

Skillbuilder Problem 2: Factors Influencing pK_a

Rank the molecules in each row from the most acidic (starting at 1) to least acidic at the indicated (*) protons. Between each pair of ordered molecules, indicate which one of the effects in the box below is *most* responsible for the difference in acidity.

Charge	Electronegativity	Polarizability	Hybridization
Resonance	Inductive	Other (specify)	

2-a.



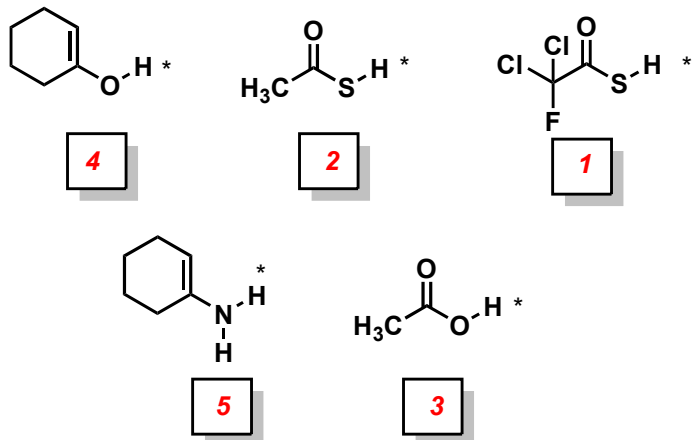
1 vs. 2: *Atom: polarizability/size*

2 vs. 3: *Hybridization Effect*
(Delocalization also possible in conjugate base)

3 vs. 4: *Atom: electronegativity*

4 vs. 5: *Atom: electronegativity*

2-b.



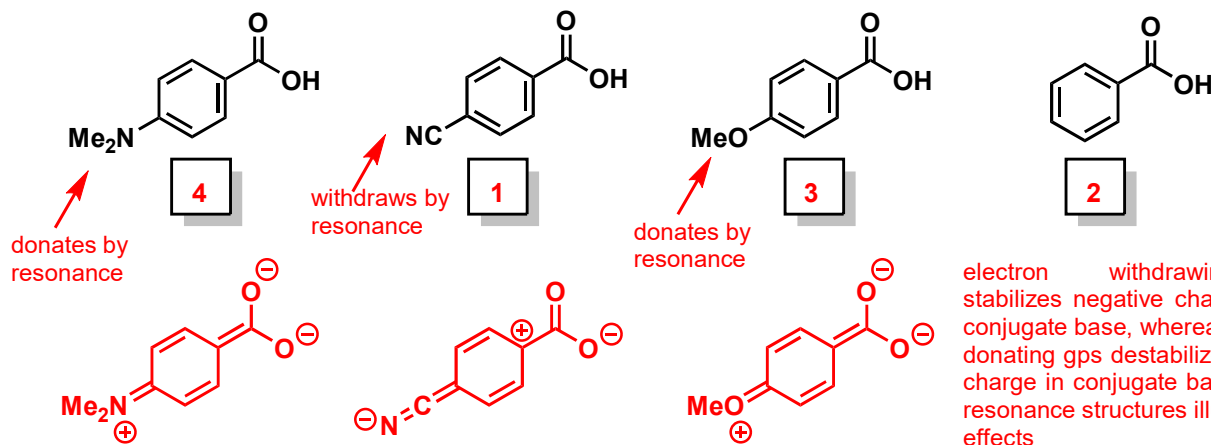
1 vs. 2: *Inductive Effect*

2 vs. 3: *Atom: polarizability/size*

3 vs. 4: *Delocalization Effect*
(atom (electronegativity) also plays a role in assessing delocalization)

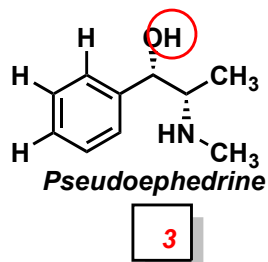
4 vs. 5: *atom: electronegativity*

2-c. All differences are due to inductive and delocalization effects; draw resonance structures to support your ranking.

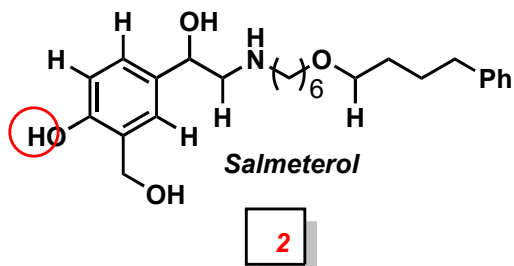


Challenge Problem 1: Acidity

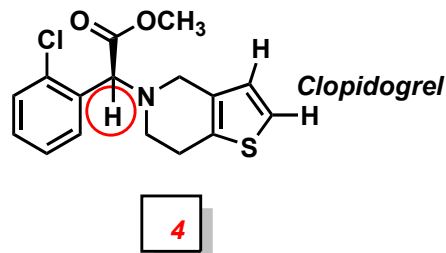
1-a. (i) Circle the most acidic atom on each of the molecules shown below; you only need to consider the hydrogens that are shown explicitly. (ii) Rank the molecules from the most acidic (starting at 1) to the least acidic (according to the most acidic site on the molecule). (iii) Between each pair of ordered molecules, indicate which one of the effects is *most* responsible for the difference in acidity.



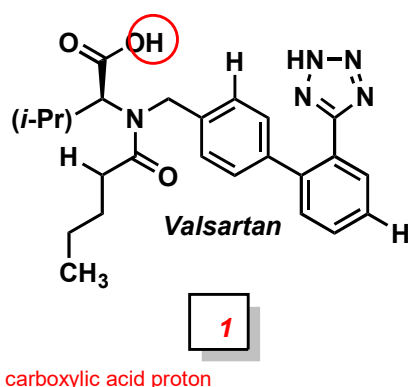
-OH more acidic than -NH, and -CH
element effect (electronegativity)



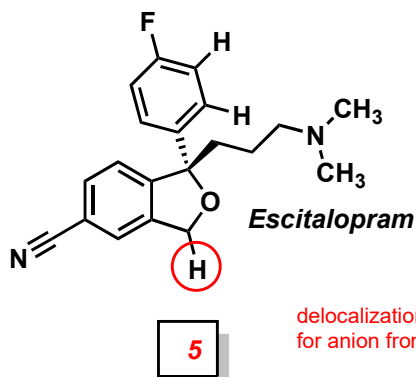
phenol -OH more acidic than alcohol
-OH's due to delocalization



anion formed by loss of circled C-H
is delocalized, others are not



carboxylic acid proton



delocalization possible only
for anion from removal of this C-H

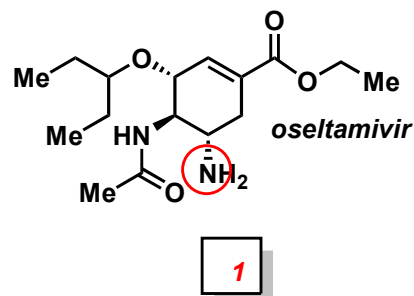
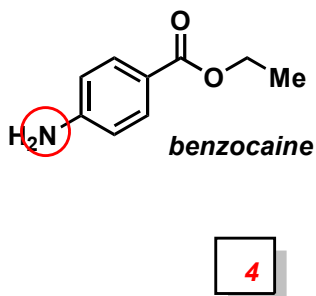
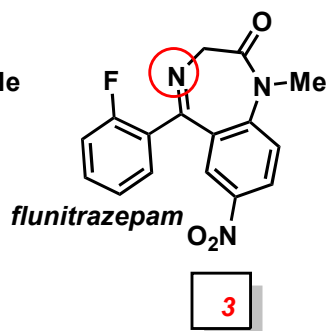
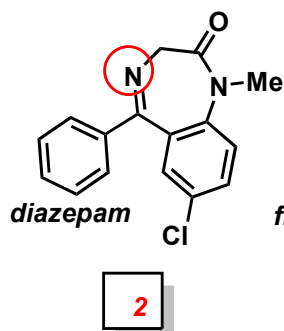
1 vs 2: resonance

3 vs 4: atom effect (electronegativity)

2 vs 3: resonance

4 vs 5: resonance (negative charge can be delocalized into
ester in clopidogrel)

1-b. Circle the most basic atom on each of the molecules shown below. Rank the molecules from the most basic (starting at 1) to the least basic (according to the most basic site on the molecule). Between each pair of ordered molecules, indicate which one of the effects is *most* responsible for the difference in basicity.



note: amide N's are less basic than non-amide N's as N lone pair in amide is involved in resonance with carbonyl gp.
sp³-N is stronger base than sp²-N.

1 vs 2: hybridization

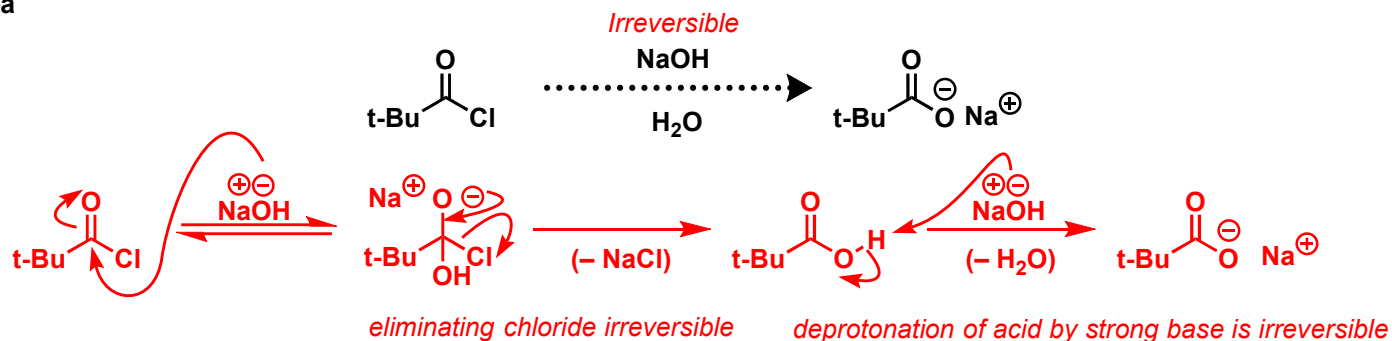
2 vs 3: inductive effects
electron-withdrawing groups
destabilize positive charge in
protonated flunitrazepam.

3 vs 4: delocalization (of N lone pair
in benzocaine, weakens base)

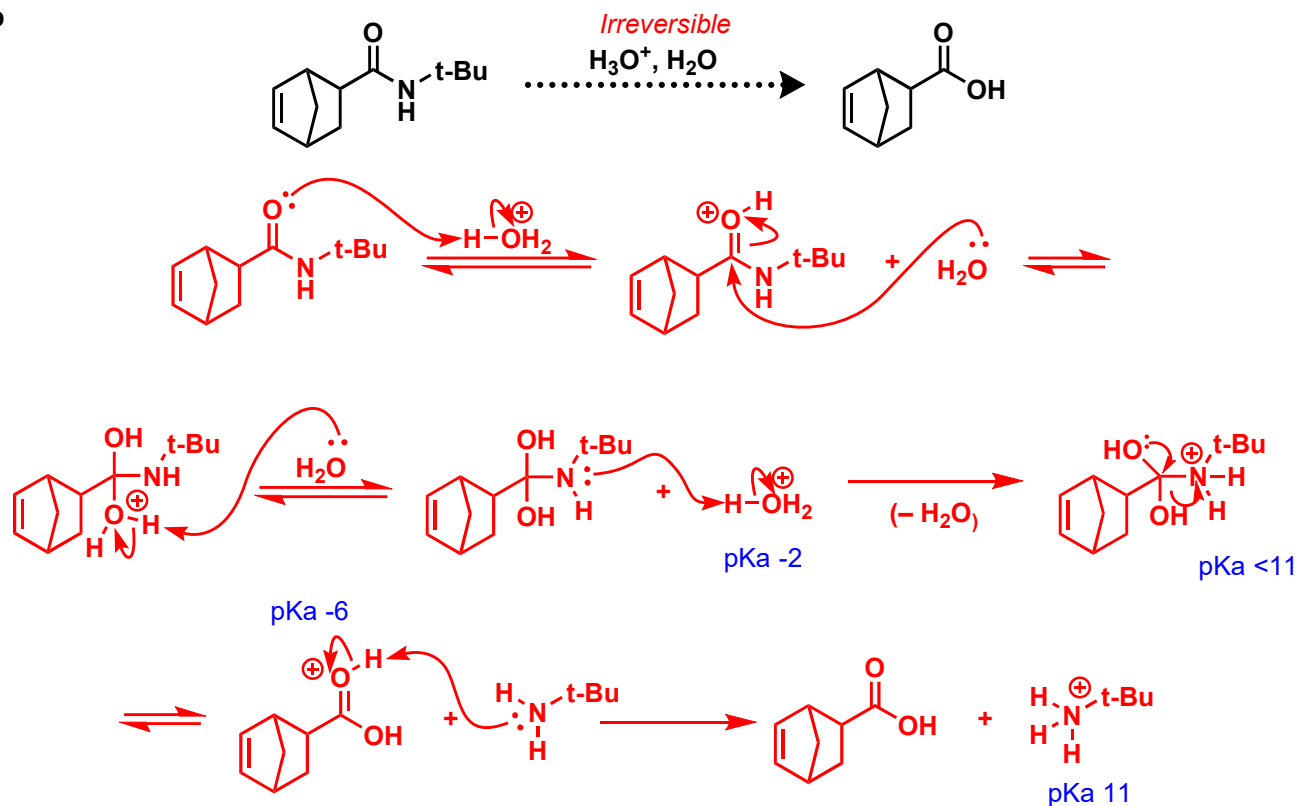
Challenge Problem 2: Acyl Transfer Reactions

Propose a mechanism for each of the transformations below, using curved arrows to represent the redistribution of electrons in each step. Indicate whether the reaction is reversible or irreversible.

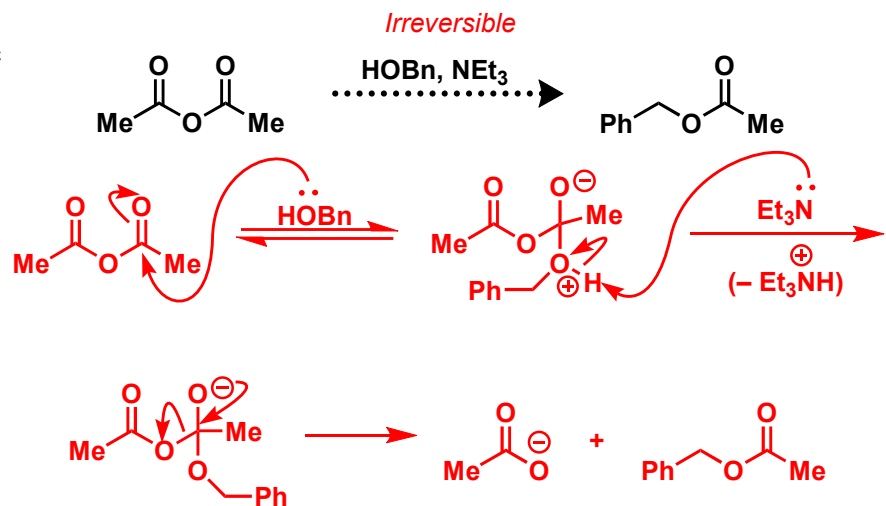
2-a



2-b

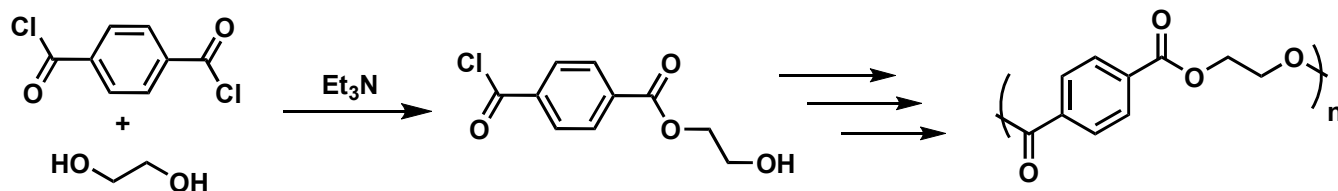


2-c

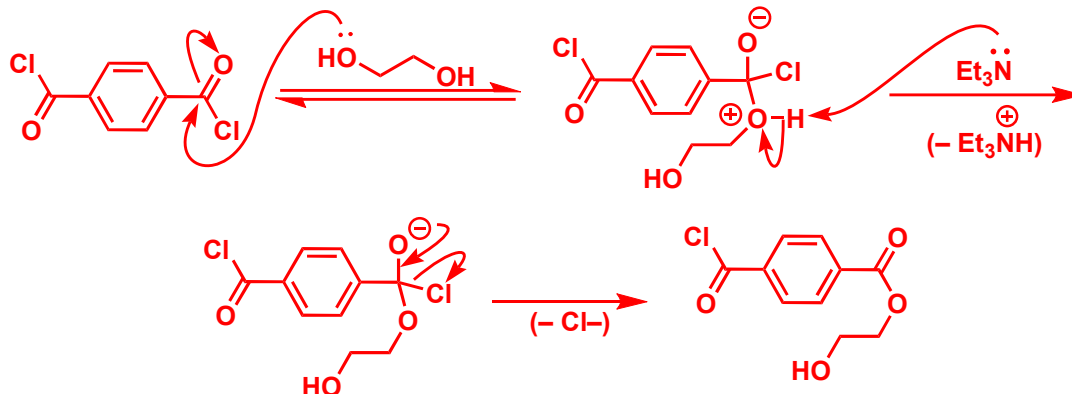


Challenge Problem 3: Acyl Transfer Reactions in Polymer Formation

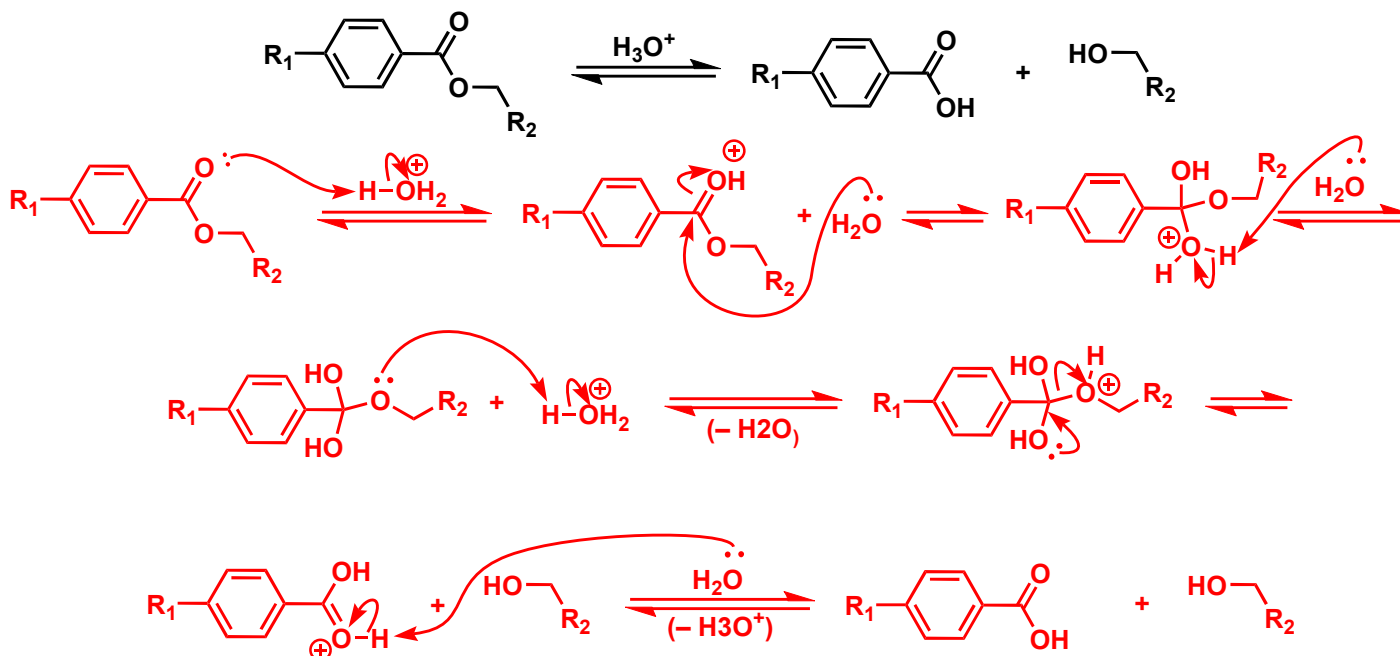
Polyethylene terephthalate (PET or "polyester") is a common synthetic polymer (plastic) used to make water bottles, clothing, and carpets. PET can be made by the process shown below. The first step is shown explicitly; reactions analogous to the first step occur repeatedly to form a very long chain with the structure at right.



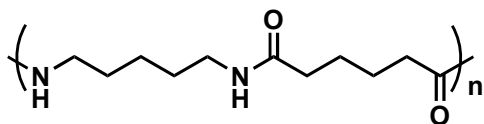
3-a. Provide a mechanism for the first step of PET production, depicted above, using curly arrows to represent the redistribution of electrons in each step.



3-b. Unlike many other plastics, PET can be destroyed by strong acid. Provide a mechanism for the degradation of PET by acid, focusing on the key ester portion of the chain shown below.



3-c. The structure of nylon, another synthetic polymer, is shown below. Predict whether nylon will be more or less resistant to acid than PET and briefly justify your answer.



Nylon will be more resistant to acid than PET because the amide carbonyl is a worse electrophile than the ester carbonyl. This is because the n_N to π^*_{CO} interaction of an amide is stronger than the n_O to π^*_{CO} interaction of an ester.